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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
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08/910,449 08/05/97 GOODWIN

R 2801-C
EXAMINER

HM11/0513

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1646
DATE MAILED:

05/13/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on _____

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

- ☒ Claim(s) 26, 27, 29-47 is/are pending in the application.
Of the above, claim(s) 26, 27, 45, 46 is/are withdrawn from consideration.
☒ Claim(s) 29 is/are allowed.
☒ Claim(s) 30-44, 47 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☒ Claim(s) 26, 27, 29-47 are subject to restriction or election requirement.

Application Papers

- ☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☐ received.
☐ received in Application No. (Series Code/Serial Number) _____
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- ☒ Notice to Comply with Sequence Rules.
☒ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☒ Notice of Draftsperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

Part III: Detailed Office Action

Notice: Effective February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit **1646**.

5

Restriction Requirement:

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 26 and 27, drawn to anti-4-1BB-L antibodies, classified in Class 530, subclass 387.1.

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II. Claims 29-44 and 47, drawn to DNA and vectors encoding 4-1BB *receptor* (4-1BB), recombinant expression of 4-1BB, 4-1BB protein, fusions thereof and dimers comprising, and pharmaceutical compositions comprising 4-1BB, classified in Class 436, subclasses 69.1, 69.7 and 320.1 as well as Class 514, subclass 2.

15

III. Claims 45 and 46, drawn to anti-4-1BB antibodies, classified in Class 530, subclass 387.1.

The inventions are distinct, each from the other because of the following reasons:

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Although there are no provisions under the section for "Relationship of Inventions" in MPEP 806.05 for inventive groups that are directed to different products or different methods, restriction is deemed to be proper because these products and/or methods appear to constitute patentably distinct inventions for the following reasons:

Inventions I and III are drawn to distinct antibodies, which antibodies are not physically or functionally related in terms of the antigen to which they bind. The antibodies are independent because each is not required for the manufacture or use of the other, and they are distinct because they are capable of separate use, each for the isolation or detection of its particular, unique antigen.

25

The proteins of Invention II are related to the antibodies of Invention III by virtue of being the cognate antigen, necessary for the production of the antibodies. Although the proteins and antibodies are related due to the necessary steric complementarity of the two, they are distinct

inventions because they are physically and functionally distinct chemical entities, and because the proteins can be used in other and materially different processes from the use for production of the antibodies, such as in pharmaceutical compositions in their own right as evidenced by claims 24 and 44, or to assay or purify the natural ligands of the proteins (as the proteins are ligand and receptor, respectively), or in assays for the identification of agonists or antagonists of the receptor protein.

The products and methods of Invention II are separate and distinct from the antibodies of Invention I wherein the two sets of products are physically, chemically and functionally distinct, and wherein the methods of Invention II neither make nor use the products of Invention I.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with Janis Henry on March 20, 1998 a provisional election was made without traverse to prosecute the invention of Group II, claims 29-44 and 47. Affirmation of this election must be made by applicant in responding to this Office action. Claims 26, 2, 45 and 46 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

Sequence Compliance:

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this

5 application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Specifically, the sequence disclosed on page 11 line 36 is not included in the sequence listing, and a sequence is listed within claim 38 without reference to the appropriate sequence identifier. Amendment of the sequence listing to include all disclosed amino acid and nucleotide sequences is required.

✓
10 **Informalities:**

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

15 X The application contains disclosure entirely outside the bounds of the elected claims. Applicant is required to modify the brief summary of the invention and restrict the descriptive matter so as to be in harmony with the claims (MPEP § 1302.01). Specifically, it is noted that the elected invention is drawn to human 4-1BB, whereas extensive portions of the specification are drawn exclusively to the cloning and characterization of 4-1BB *ligand*.

20 **Objections and Rejections under 35 U.S.C. §112:**

Claims 30-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

25 Claims 30 and 41 are indefinite for use of parentheses surrounding the phrase "amino acids 1-163 of SEQ ID NO: 7". It cannot be determined whether said amino acids 1-163 comprises a
✓ limitation defining the extracellular domain, or whether alternatively that sequence is merely exemplary of a species of the human 4-1BB extracellular domain.

30 ✓ Claims 32-34 are indefinite because there is no antecedent basis in claims 29-31 (from which they depend) for "a DNA *sequence*". Deletion of the word "sequence" would be remedial.

Claim 38 is indefinite because the metes and bounds of a "human 4-1BB polypeptide" cannot be determined. Specifically, the Examiner notes the specification at page 3 which states "The present invention provides full length 4-1BBL and 4-1BB polypeptides as well as biologically active fragments and variants thereof." Further, the specification at page 8 states "The variant sequences
5 differ from a native nucleotide or amino acid sequence by one or a plurality of substitutions, deletions or additions..." Given the specification, the Examiner cannot determine whether claim 38 is intended to be limited to full-length, naturally occurring human 4-1BB, or alternatively, is intended to encompass fragments and derivatives of such.

Claim 40 is indefinite as the metes and bounds of the claim cannot be determined. The claim
10 allows an unspecified number of conservative amino acid substitutions. The claim is therefore indefinite as it is not clear how many such substitutions may be made.

Claim 41 is indefinite (in addition to the reasons cited above) for the recitation that the fragment is "capable of" binding "a 4-1BB-L". With respect to the former phrase, it is not clear what applicants intend by "capable of"; either the fragment binds, or it does not. Amendment to positively
15 recite that the fragment binds to 4-1BB Ligand would be remedial. With respect to the recitation "a 4-1BB-L", it is not clear whether applicants intend a naturally occurring 4-1BB ligand, or alternatively whether the language encompasses *any* moiety that binds to 4-1BB.

Claim 44 is indefinite because in the absence of any intended use it cannot be determined what amount would be "effective", nor what type of diluent, carrier or excipient would be "suitable".

20 Claims 31, 35-37, 39, 42 and 43 are rejected as depending from an indefinite claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

25 The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 38, 40, 44 and 47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for human 4-1BB and nucleic acids encoding such, as well as

fragments of 17+ nucleotides which are fragments of SEQ ID NO: 7, does not reasonably provide enablement for all "4-1BB polypeptides" comprising the sequence recited in claim 38, nor all conservative variants of amino acids 1-232 or 1-163 of SEQ ID NO: 7 (claim 40), nor of any ✓ pharmaceutical composition comprising human 4-1BB (claim 44), nor all fragments of at least 17
5 nucleotides of the DNA of claim 29 (claim 47). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Claim 38 encompasses all possible variants of 4-1BB which have the recited N-terminal sequence. However, as stated in the rejection under 35 U.S.C. §112, second paragraph, above, it is
10 not clear what the metes and bounds of the claim are, such that the claim encompasses any protein having that N-terminal sequence. The specification does not teach how to use a commensurate number of such species, of which a substantial proportion would not retain the property of binding
✓ to 4-1BB ligand. It would require undue experimentation to determine how to use the species which do not retain such binding function or alternatively are not useful for the production of antibodies to
15 the protein of SEQ ID NO: 7, as the specification as filed gives no guidance as to how to use such species. With respect to claim 40, the claim allows conservative substitutions in the protein of SEQ ID NO: 7, but specifies no function to be retained. While the person of ordinary skill in the art would be able to make such species, the specification does not, as was found for the species of claim 38,
above, teach how to use such species which do not retain the ability to bind to 4-1BB ligand or
20 alternatively are not useful for the production of antibodies to the protein of SEQ ID NO: 7, as the specification as filed gives no guidance as to how to use such species.

The specification as filed does not enable the scope of pharmaceutical compositions
✓ comprising a protein comprising the extracellular domain of 4-1BB. The recitation of "pharmaceutical composition" implies an intended use as a pharmaceutical, for which the specification
25 provides no enablement. There has been disclosed no disease or condition which can be treated by administration of 4-1BB, nor any condition that may be diagnosed using 4-1BB. Therefore, it would require undue experimentation to determine how to use such a pharmaceutical composition. It is

noted that amendment of claim 44 to claim simply a composition comprising the soluble human 4-1BB polypeptide of claim 41 would be remedial in regard to this grounds of rejection.

Finally, enablement is not commensurate in scope with claim 47, which is drawn to fragments of at least about 17 nucleotides of the DNA of claim 29, and which encompasses all degenerate variants of the sequence of nucleotides 120-884 of SEQ ID NO: 7. While enablement is commensurate in scope with all such fragments which are fragments of SEQ ID NO: 7, enablement is not commensurate in scope with all such fragments of degenerate variants of SEQ ID NO: 7. Such fragments are generally considered to be useful as hybridization probes, or for use as primers, e.g. in a PCR reaction or alternatively for the recombinant production of an antigenic portion of the encoded protein (to be used for the production of antibodies). However, large numbers of the encompassed degenerate variants would not hybridize to naturally occurring 4-1BB sequences under the conditions commonly used for hybridization of priming a synthesis reaction, and further would not encode an antigenic portion of the disclosed protein and therefore the specification as filed does not teach how to use such fragments as would not be expected to be useful for those purposes.

Prior Art:

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Kwon et al. (PNAS 86:1963) disclose the sequence of murine 4-1BB. The introduction of the paper states that 4-1BB was derived from a set of human T-cell specific cDNA clones. However, Kwon et al. (PNAS 84:2896), to which reference is made for such clones, clearly indicates that the origin of the clones was murine, and not human cell lines. With particular respect to claim 47, there are several regions of Kwon's sequence which differ from that claimed by only a single nucleotide in a stretch of over 17 nucleotides of what would otherwise constitute identity; however, in each of those regions, the single nucleotide difference is non-silent, that is, results in a change in the amino acid sequence encoded, and thus does not fall within the metes and bounds of the claim.

Chalupny et al., PNAS 89:10360 (1992), discloses that 4-1BB binds to extracellular matrix proteins.

Kwon et al., Cellular Immunology 121:414 (1989) discloses that a human homologue of clone L2G25B, which was obtained via similar methodology as 4-1BB, had been identified, but does not
5 make an equivalent disclosure for 4-1BB.

Advisory Information:

Claim 29 is allowable. Claims 30-44 and 47 would be allowable if amended to overcome the
10 above rejections under 35 U.S.C. §112, first and/or second paragraphs.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 8:00 A.M. to 4:30 P.M.

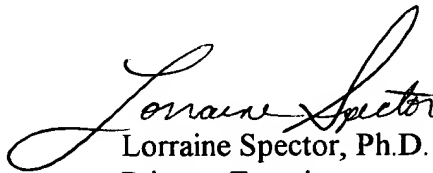
15 If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Stephen Walsh, can be reached at (703)308-2957.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

20 Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by
25 applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 305-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. Please advise the Examiner at the telephone number above when an informal fax is being transmitted.

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Lorraine Spector, Ph.D.
Primary Examiner

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